REMARKS

Claims 1, 2 and 5-8 are pending in the application. Claims 3 and 4 are canceled. Claims 1, 2, 5, 6, and 7 are amended. Applicants reserve the right to pursue any withdrawn or canceled subject matter in one or more continuation or divisional applications.

Rejections under 35 U.S.C. §112

The Examiner has rejected claims 1-8 under 35 U.S.C. §112 second paragraph as indefinite because it is allegedly unclear to whom the compound is being administered. The claims have been amended to recite that the compound is administered to "a human patient in need thereof" to overcome this rejection.

The Examiner has also rejected claim 1 for the recitation "optionally substituted." It would be clear to one skilled in the art that the residue of an amino acid, as described on page 5, lines 12-15, can be optionally substituted.

The Examiner has also rejected claim 1 stating that it is not clear whether Ile represents a substitution on another amino acid or a different substitution for R_1. The claims have been amended to clarify that residue R_1 is, alternatively, a residue that is "derived from Ile."

Prior Art Rejections under 35 U.S.C. §§ 102 and 103

The Examiner has rejected claims 1, 3-4 and 7 under 35 U.S.C. §102(b) and claims 1-8 under 35 U.S.C. §103(a) over Masuyama, et al. (US 6,410,685).

The '685 patent is directed to the treatment of stress using certain tripeptides, namely either Ile-Pro-Pro or Val-Pro-Pro. Amended claims 1, 2, 5-10 and 16 are directed to the treatment of postlesional diseases of ischemic, traumatic or toxic origin by administration to a patient in need thereof of certain proline-derivative tripeptides, defined in the amended claims.

The compounds recited in the amended claims are not disclosed in the '685 patent. The '685 patent discloses only certain tripeptides that are either Ile-Pro-Pro or Val-Pro-Pro. The amended claims recite proline derivatives with R_1 and R_2 that are residues derived from Phe or Ile (R_1) and Gly or Ile (R_2). The amended claims do not include compounds that are described by the '685 patent.

These claims are also not rendered obvious by the disclosure of a different set of compounds in the '685 patent. The '685 patent focuses exclusively on two peptides that differ from those in the amended claims for the treatment of physiological stress. The '685 patent does not disclosure or suggest the use of any tripeptides for the treatment of postlesional diseases of ischemic, traumatic or toxic origin. A skilled artisan would have no way to identify the compounds described in the amended claims for the treatment of postlesional diseases based on a disclosure of *different* compounds for the treatment of a *different* condition. The utility of the compounds recited in the amended claims is apparent from the examples in the disclosure which show that the recited compounds have effect on nerve sprouting, as described in Example 6. The disclosure of the '685 patent therefore does not suggest either the pharmaceutical compositions or methods of treatment of postlesional diseases of ischemic, traumatic or toxic origin with the proline-derived compounds recited in the amended claims.

The Examiner has also rejected claims 1-6 under 35 U.S.C. §102(b) and claims 1-8 under 35 U.S.C. §103(a) over Yoshimasa, et al. (JP 09169797).

The '797 application describes the use of certain peptides with protease activator activity. The abstract of the '797 patent describes peptides of formula I, namely Pro-A-B where A is Phe, Lys, Asn, Tyr or Thr; B is Pro or Trp (see abstract). In contrast, the amended claims recite proline derivatives with two other amino acid residues that are derived from Phe or Ile (R_1) and Gly or Ile (R_2). The amended claims do not include compounds that are described in the '797 application. As discussed above, there is no way to predict that the compounds of the amended claims could be effective for treatment of postlesional diseases of ischemic, traumatic or toxic origin based on a disclosure of *different* compounds for the treatment of a different condition.

The disclosure of the '797 application therefore neither teaches nor suggests either the compositions or methods of treatment of the amended claims.

Claims 1-6 are rejected under 35 U.S.C. § 102(b) and claims 1-8 under 35 U.S.C. §103(a) over Yoshimasa, et al. (JP 09040577).

The '577 application describes compositions of tripeptides that are Pro-A-B where A is phenylalanine, lysine, etc. and B is proline or tryptophan (see abstract). The Examiner specifically indicates tripeptides of formula I that are Pro-Phe-Pro and Pro-Phe-Pro-NH_2. As described above, the compounds recited in the amended claims are not described in the '577 application. The amended claims recite proline derivatives with R_1 and R_2 that are residues derived from Phe or Ile (R_1) and Gly or Ile (R_2). The '577 application therefore does not teach the compounds of the amended claims. As discussed above, the disclosure of *different* compounds for the treatment of different conditions also does not suggest either the methods or the pharmaceutical compositions of the amended claims, as a skilled artisan would have no guidance for the development of treatments for postlesional diseases of ischemic, traumatic or toxic origin with compounds of the amended claims, and would have no way to predict that any tripeptide compound would be useful for the treatment of such diseases based on the '577 application.

The Examiner has also rejected claims 1-6 under 35 U.S.C. §102(b) and claims 1-8 under 35 U.S.C. §103(a) over Hathaway (WO 92/13549).

The '549 publication generally describes hydrophobic peptides for the inhibition of cell proliferation. Although a large generic genus of peptides is described in the specification, no specific disclosure teaches the peptides covered in the amended claims, namely compounds in which R_1 is a residue derived from Phe or Ile and R_2 is a residue derived from Gly or Ile. The '549 provides no specific teaching of the proline-derivatives recited in the amended claims in which R_1 is a residue derived from Phe or Ile and R_2 is a residue derived from Gly or Ile.

The '549 specification also does not suggest the use of the compounds recited in the amended claims, as the specific disclosure is directed to peptides have carboxy-terminal amino acids that are aldehyde derivatives of Leu, Lys, nLeu, Phe or Tyr (page 11, lines 14-16) and the most preferred peptides are leucine derivatives (page 11, lines19-20). The '549 publication also does not suggest that any tripeptides could be useful for the treatment of postlesional diseases of ischemic, traumatic or toxic origin, let alone the tripeptides recited in the amended claims. The '549 publication teaches that certain tripeptides are allegedly useful for the inhibition of cell proliferation. This is taught as being particularly useful for the treatment of cancer, prostatic hypertrophy, arteriosclerosis, etc. It would have been counterintuitive for a skilled artisan to use any compounds that are taught to prevent cell proliferation when trying to treat postlesional diseases of ischemic, traumatic or toxic origin, which are related to the cell death. The utility of the compounds of the amended claims is apparent from the disclosure in the present application. The '549 publication therefore, insofar as it teaches tripeptides for the use in any diseases, *teaches away* from the use of any of these peptides for the treatment of postlesional diseases. Therefore, the '549 publication does not suggest the use of the compounds recited in the amended claims in any compositions, nor does it suggest the use of any tripeptides, particularly not those recited in the amended claims, for the treatment of postlesional diseases of ischemic, traumatic or toxic origin.

The Examiner also rejects claims 1 and 3-7 under 35 U.S.C. §102(b) and claims 1-8 under 35 U.S.C. §103(a) over Maruyama et al. (EP 0445606).

The '606 patent describes certain tripeptides that are allegedly angiotensin converting enzyme inhibitors that are generally of the formula: Leu-Xaa-Pro where Xaa is Gly, Ala, Val, Ile, Thr, Asp, Glu, Lys, Orn, Cys, Met, Phe, Tyr, Trp, His or a hydroxyproline residue or are Leu-Ser-Pro, Leu-Gln-Pro, Val-Ser-Pro, Leu-Leu-Pro, Leu-Asn-Pro, Phe-Leu-Pro, Leu-Ala-Ala, Val-Ala-Ala, Leu-Gln-Gln, Val-Ala-Tyr, Leu-Ala-Tyr, Leu-Ser-His, Ile-Arg-Ala, Leu-Arg-Pro. The amended claims recite proline-derived tripeptide compounds in which R_1 is a residue derived from Phe or Ile and R_2 is a residue derived from Gly or Ile. The '606 patent does not teach or suggest the compounds recited in the amended claims. Furthermore, the '606 patent

does not teach or suggest the use of any tripeptides for the treatment of postlesional diseases of ischemic, traumatic or toxic origin, and instead focuses on hypertension and other diseases related to the renin-angiotensin system. There is therefore no suggestion in the '606 patent of either the compositions or methods of treatment recited in the amended claims.

The Examiner has also rejected claims 1-14, 16 and 17 under 35 U.S.C. §103(a) over Hathaway or Maruyama in view of Yoshimasa et al. None of the primary references render obvious the amended claims, and the secondary reference teaches neither the specific compounds, nor the methods of treatment of neurodegenerative diseases recited in the amended claims.

Double Patenting

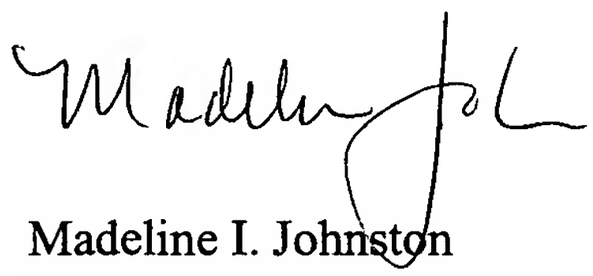
The Examiner has provisionally rejected claims 1-8 under the judicially created doctrine of obviousness-type double patenting over claims 1-10 and 16 of copending Application no. 10/635,797. The Examiner has apparently equated the treatment of postlesional diseases of ischemic, traumatic or toxic origin disclosed in the pending application with the treatment of neurodegenerative diseases disclosed in the '797 application.

Contrary to the Examiner's assertion, these claims do not cover overlapping subject matter. A postlesional disease of toxic origin, as recited in the pending application, is *not* the same a neurodegenerative disease and *does not* encompass Alzheimer's disease or amnesia. A postlesional disease of toxic origin is induced by exogenous toxins such as alcohol, drugs, heavy metals, etc. In support of this, Alzheimer's disease and postlesional diseases of toxic origin are differently classified by the World Health Organization. Alzheimer's is classified in block 30 of the International Statistical Classification of Diseases and Related Health Problems (see www.who..int/whosis/icd10/) while postlesional diseases of toxic origin (i.e. intoxication) are classified as 'injury' in block S. A skilled person therefore can clearly distinguish Alzheimer's disease form a postlesional diseases of toxic origin.

The Examiner has also indicated that amnesia is considered a postlesional diseases of traumatic origin. However, amnesia is not a specific disease, but instead is a *symptom* that can have its origin both in neurodegenerative diseases such as Alzheimer's disease or can be induced, for example, by administering drugs such as scopolamine, diazepam or barbital. Amnesia is not associated with (necrotic) cell death so that its treatment does not require nerve regeneration, but instead it is a reversible cognitive impairment.

Applicants believe no further fees are due with this response, however if the Examiner determines that any fees are due, the Commissioner is hereby authorized to charge any additional fees associated with this response to Deposit Account No. 11-0980.

Respectfully submitted,



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